PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
Case 889/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU 03/00041	11.06.2003	14.06.2002
International Patent Classification (IPC) or both national classification and IPC		
C07D451/04		
Applicant		
SANOFI-SYNTHELABO et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.12.2003	12.05.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Steendijk, M Telephone No. +49 89 2399-8460

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU 03/00041

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-13, 15, 16, 18, 20, 22-83	as originally filed
14, 17, 19, 21	received on 29.04.2004 with letter of 26.04.2004

Claims, Numbers

1-20	as originally filed

Drawings, Sheets

1/4	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 14-20

   because:

   ☒ the said international application, or the said claims Nos. 14 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 15-20

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

see separate sheet

1) The present application relates to DPP-IV inhibitors of formula I (claims 1-14) as well as intermediates comprising either the azabicyclic ring B or the proline analogue Z (claims 15-20).
No additional search fees were paid for claims 15-20 following an invitation in accordance with R 40 PCT. No preliminary examination can be carried out for the matter not covered by the search report.

2) The following documents are cited herein:

D1 : WO-A-98 19998
D2 : WO-A-01 34594
D3 : EP-A-1 323 710
D4 : WO-A-01 96295
D5 : US-A-4 273 778
D6 : WO-A-03 02553

Document D6 was published after the claimed priority date; on the presumption that the priority is valid, this document is not regarded as prior art.

3) Novelty (claims 1-14)
Documents D1-D4 describe DDP-IV inhibitors derivatives which differ from the presently claimed compounds of formula I in the presence of a different group at the position of the azabicyclic ring B.
Document D5 describes intermediates comprising an azabicyclic-amine, which lack the specific proline-like group Z.

It is noted that document D6 describes DDP-IV inhibitors derivatives comprising an azabicyclic ring; the compounds of D6 differ, however, in the further subsitutions.

4) Inventive step (claims 1-14)
Documents D1-D4 may be considered to represent the closest prior art; the structurally nearest compounds are those carrying a piperidine in stead of an azabicyclic ring for B.
The applicant has provided comparative date with respect to compound of the closest prior art indicating that the bicyclic analogues presently claimed provide for

a particular high level of activity (IC50 below 20 nM in Caco-2 test), which would seem the more surprising as the tested pyrolidine/piperidine analogs tend to lower activities than the open chain derivatives.
Accordingly, as solution to the problem of providing further and improved DDP-IV inhibitors, the claimed subject-matter may not be considered obvious.

5) Further observations
Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

The claims rely on the drawings for the definition of the subject-matter; the claims should, however, be clear per se.

Example 1.

(4*R*)-3-(2-{[8-(2-Pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl]*exo*-amino}acetyl) thiazolidine-4-carbonitrile

The meaning of R is 2-pyrimidinyl group, B means a group of formula (1), Z means a group of formula (A) in general formula (I).

a.) *tert*-Butyl 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate with the general formula (V) - where R and B are given above, Y is *tert*-butoxycarbonyl group

14,7 g (65 mmol) of *tert*-butyl 8-benzyl-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate (*J. Med. Chem.* **1991,** *34,* 656) and 8,93 g (78 mmol) of 2-chloropyrimidine and 12,7 ml (85 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene were dissolved in 230 ml of *n*-pentanol and heated under reflux for 4 hours. The solvents were evaporated and the residue was dissolved in 250 ml of chloroform and washed with 2x300 ml of water, dried over sodium sulfate, and purified by column chromatography using *n*-hexane - ethyl acetate- chloroform (1:1:1) as eluent to result in white crystals which were triturated with *n*-hexane. Yield: 13,25 g (67%). M.p.: 113-115°C. ^{1}H-NMR ($CDCl_3$): δ 1.34 (s, 9H), 1.49 (t, 2H), 1.66-1.97 (m, 6H), 3.89 (br, 1H), 4.61 (d, 2H), 6.60 (t+br, 1+1H), 8.34 (d, 2H).

b.) 8-(2-Pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-amine with the general formula (II), where R and B are given in step 1a.)

13 g (43 mmol) of *tert*-butyl 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate was dissolved in a mixture of 120 ml of trifluoroacetic acid and 120 ml of dichloromethane. The solution was stirred for 30 minutes and evaporated. The residue was dissolved in 50 ml of dichloromethane and evaporated. This method was repetead three

g.) (4*R*)-3-(2-{[8-(2-Pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl]*exo*-amino} acetyl)thiazolidine-4-carbonitrile

245 mg (1,2 mmol) of 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-amine and 191 mg (1 mmol) of (4*R*)-3-(2-chloroacetyl)thiazolidine-4-carbonitrile and 0,42 ml (3 mmol) of triethylamine were dissolved in 20 ml of dry acetonitrile and stirred at 70°C for 4 hours and then at room temperature overnight. Then the mixture was evaporated to give a yellow thick oil which was purified by column chromatography using chloroform-methanol (9:1) as the eluent to result in a solid white product which was crystallized from diethyl ether. Yield: 191 mg (53%). M.p.: 135-136°C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.33 (td, 2H), 1.6-2.0 (m, 5H), 3.05 (tt, 1H), 3.32 (m, 2H), 3.44 (ddd, 2H), 4.63 (s, 2H), 4.56 (d, 1H), 4.61 (m,2H), 4.70 (m,1H), 5.23 (dd, 1H), 6.60 (t, 1H), 8.33 (m, 2H).

Example 2.

(4*R*)-3-(2-{[8-(5-Cyanopyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl]-*exo*-amino} acetyl)thiazolidine-4-carbonitrile dihydrochloride

In the general formula (I) R stands for 5-cyanopyridin-2-yl group, B means for the group of formula (1), Z stands for the group of formula (A).

a.) *tert*-Butyl 8-(5-cyanopyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate with general formula (V), where R and B are given above, Y is *tert*-butoxycarbonyl group

The solution of 415 mg (3 mmol) of 2-chloro-5-cyanopyridine, 679 mg (3 mmol) of *tert*-butyl 8-benzyl-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate and 0,46 ml (3,1 mmol) of diazabicyclo[5.4.0]undecene in 25 ml of *n*-pentanol was refluxed for 8 hours. The resulting solution was evaporated in vacuum, the residue was dissolved in dichloromethane, washed with water and dried over sodium sulfate. After purification by chromatography using *n*-

precipitation with diethyl ether the title compound was obtained in the form of white crystals: 75 mg (32 %), mp: 204-206°C. ^{1}H-NMR (DMSO-d_6): δ 1.70-1.78 (m, 4H), 2.01 (m, 4H), 3.37 (m, 2H), 3.67 (m, 1H), 4.07 (m, 1H), 4.21 (m, 1H), 4.56 (d, 1H), 4.76-4.79 (m, 3H), 5.33 (m,1H), 6.89 (d, 1H), 7.91 (dd, 1H), 8.53 (d, 1H), 9.01 (bs, 2H).

Example 3.

(4*R*)-3-(2-{[8-(2-Pyrazinyl)-8-azabicyclo[3.2.1]oct-3-yl]*exo*-amino}acetyl) thiazolidine-4-carbonitrile dihydrochloride

The meaning of R is 2-pyrazinyl group, B means a group of formula (1), Z means a group of formula (A) in general formula (I).

a.) *tert*-Butyl 8-(2-pyrazinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate

with the general formula (V) - where R and B are given above, Y is *tert*-butoxycarbonyl group

0,54 ml (6 mmol) of chloropyrazine, 1,13 g (6 mmol) of *tert*-butyl 8-benzyl-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate and 0,97 ml (6,5 mmol) of 1,8-diaza-bicyclo[5.4.0]undec-7-ene were dissolved in 40 ml of *n*-pentanol and heated under reflux for 50 hours. The solvent was evapotared, the residue was dissolved in 50 ml of chloroform, washed with 4x30 ml of water, dried over sodium sulfate, and purified by column chromatography using *n*-hexane - ethyl acetate - chloroform (3:1:1) as eluent to result in white crystals which was triturated with *n*-hexane. Yield: 0,55 g (36 %). M.p.: 122-123°C. ^{1}H-NMR (DMSO-d_6): δ 1.34 (s, 9H), 1.44-1.66 (m; 2H), 1.67-1.99 (m, 6H), 3.88 (m, 1H), 4.56 (bs, 2H), 6.59 (d, 1H), 7.77 (d, 1H), 8.07 (dd, 1H), 8.17 (d, 1H).

Example 4.

(2*S*)-1-(2-{[8-(5-Nitropyridin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl]-*exo*-amino}acetyl)pyrrolidine-2-carbonitrile

The meaning of R is 5-nitropyridin-2-yl group, B means a group of formula (1), Z means a group of formula (B) in general formula (I).

a.) *tert*-Butyl 8-(5-nitropyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate with (V) general formula, where R and B are given above, Y is *tert*-butoxycarbonyl group

476 mg (3 mmol) of 2-chloro-5-nitropyridine, 679 mg (3 mmol) of *tert*-butyl 8-benzyl-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate and 0,46 ml (3,1 mmol) of 1,8-diazabicyclo [5.4.0]undec-7-ene were dissolved in 25 ml of *n*-pentanol and heated under reflux for 1 hour. The solvent was evapotared, the residue was dissolved in 40 ml of chloroform, washed with 4x40 ml of water, dried over sodium sulfate and evaporated. The solid residue was triturated with diethyl ether to result in yellow crystals. Yield: 731 mg (70 %). M.p.: 212-214°C. ^{1}H-NMR (DMSO-d_6): δ 1.34 (s, 9H), 1.41-1.54 (m; 2H), 1.81-2.16 (m, 6H), 4.00 (m, 1H), 4.75 (bs, 2H), 6.63 (d, 1H), 6.82 (d, 1H), 8.21 (dd, 1H), 8.98 (d, 1H).

b.) 8-(5-Nitropyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-amine with general formula (II), where R and B are given in step 4a.)

651 mg of *tert*-butyl 8-(5-nitropyridin-2-yl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate (1,87 mmol) was dissolved in 20 ml of 12% ethanolic hydrochloric acid and the solution was stirred for 3 hours. Under cooling 90 ml 1*N* sodium hydroxide was added to the formed a suspension which was extracted 4 x 50 ml dichloromethane. The layers were separated, the organic phase was dried, evaporated and the residue was triturated with *n*-